

Reviews

Adjunctive Low Molecular Weight Heparin During Fibrinolytic Therapy in Acute ST-Segment Elevation Myocardial Infarction: A Meta-Analysis Of Randomized Control Trials

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ABSTRACT

Background: Recent data suggests that low molecular weight heparins (LMWHs) may be superior to unfractionated heparin (UFH) as an adjunct to fibrinolytic therapy in patients with acute ST-segment elevation myocardial infarction (STEMI).

Hypothesis: We evaluated cardiac outcomes and the risk of major bleeding with LMWHs vs UFH in the management of STEMI.

Methods: Seven randomized trials of patients with acute STEMI treated with fibrinolytic therapy and adjunctive LMWHs through the index hospitalization or weight-based UFH for at least 48 hours were identified. We analyzed both primary endpoints (death and nonfatal recurrent myocardial infarction through 30 days), and secondary endpoints (death, recurrent myocardial infarction, and major bleeding during index hospitalization at 7 days). Outcomes were computed using the Mantel-Haenszel fixed-effect model. A 2-sided alpha error of <0.05 was considered significant.

Results: Compared to UFH, LMWH significantly reduced reinfarction ($p < 0.001$) during hospitalization at 7 days and the effect remained consistent at 30 d ($p < 0.001$). When analyzed for mortality at 7 days and 30 days follow-up, there were no statistically significant differences observed between the 2 groups. Additionally the LMWH group had higher risk of major bleeding ($p < 0.001$).

Conclusions: The present meta-analysis suggests in patients receiving fibrinolytic therapy for STEMI, LMWHs as an adjunctive therapy is superior to UFH in reducing reinfarction during hospitalization at 7 days and at 30 days. The mortality was not significant between the 2 groups during hospitalization at 7 days and at 30 days. However, UFH is superior to LMWHs in the reduction of major bleeding at 7 days index hospitalization.

Introduction

Current literature suggests the role of inflammation in the pathophysiology of coronary atherosclerosis.¹ Nevertheless, formation of thrombus at the site of atherosclerotic plaque causing narrowing of coronary arteries remains the basis of acute coronary syndrome.² Fibrinolytic therapy given during acute myocardial infarction (AMI) can cause activation of coagulation cascade by release of thrombin bound to the clot. This may further lead to re-occlusion of coronary arteries. Use of intravenous heparin has been found to reduce the increased thrombin activity associated with thrombolysis.³ Even though intravenous heparin does

not inhibit thrombin production;³ most of the physicians continue using it as an adjuvant to fibrinolytics in the treatment of AMI.⁴

A recent meta-analysis published in 2005 by Eikelboom et al., suggests that low molecular weight heparin (LMWH) may be a preferable antithrombotic agent in aspirin treated patients with ST-segment elevation myocardial infarction (STEMI). When compared with unfractionated heparin (UFH) it was found to reduce the rate of reinfarction by almost half.⁵ In 2006, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment—Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial⁶ comparing enoxaparin and UFH was published. This study involved a large population of 20,506 patients with STEMI. The purpose of the current meta-analysis was to analyze if the addition of newer studies with substantial numbers of patients provides different results.

There was no financial support received to carry out the above study. There has been no commercial or proprietary interest in any drug, device, or equipment mentioned in the submitted article.

Methods

Identification

A literature search for prospective randomized clinical trials in STEMI comparing subcutaneous LMWH versus intravenous UFH as an antithrombotic agent was performed. Formal computer aided searches of electronic databases (MEDLINE, PubMed, Cochrane Controlled Trials Registry) by scrutiny of the reference lists of trials and review articles, abstracts, meeting proceedings, and the manufacturers of heparins (including LMWH and UFH) from January 1975 to July 2007 were performed. The keywords used were: anticoagulants, acute myocardial infarction, ST-segment elevation myocardial infarction, randomized controlled trial, in combination with generic and trade names of individual LMWHs and fibrinolytic agents.

Selection of Trials

Inclusion Criteria: All trials had to meet all the following criteria to be included in the analysis:

1. Randomized trials
2. Include patients with acute ST-segment elevation myocardial infarction (STEMI) who received aspirin and fibrinolytic therapy.
3. Compare subcutaneous LMWH with intravenous UFH as an adjunctive antithrombotic therapy
4. Reported death, reinfarction, and bleeding as outcomes during in-hospital or at approximately day 7 and at day 30.
5. Follow-up periods varied for the different trials ranging from 5 days to 3 months.

Exclusion Criteria: Trials that did not meet the above criteria were excluded. These included trials that compared LMWH or UFH-treated patients with untreated patients or placebo groups for direct comparison of primary endpoint.^{7–14}

Data Extraction

On the basis of the above set criteria, 7 randomized trials of patients with acute STEMI treated with aspirin, fibrinolytic therapy, and adjunctive LMWHs through the index hospitalization or weight-based UFH for at least 48 h were identified^{6,15–20} (Table 1). A meta-analysis from these studies consisting of 27,604 patients was performed. We analyzed the primary endpoint (death and nonfatal recurrent myocardial infarction through 30 days) and secondary endpoint (death, recurrent myocardial infarction, and major bleeding during index hospitalization at 7 days). As the large size of the TIMI-EXTRACT 25 ($n = 20,506$) could influence the overall estimates of the above meta-analysis ($n = 27,604$), we performed a second meta-analysis excluding the TIMI-EXTRACT 25 to see if our meta-analysis was overly affected by the dominant representation of this trial.

Definitions

Acute coronary syndrome (ACS; ST-segment elevation and depression, Q-wave and non-Q-wave, as well as, unstable angina) has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischemia.²¹

The primary efficacy endpoint was the composite of death from any cause or nonfatal recurrent myocardial infarction in the first 30 d after randomization. The secondary endpoint was composite of death from any cause, nonfatal MI, and major bleeding, all during index hospitalization or approximately at 7 d. Major bleeding defined using TIMI criteria as intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss leading to hemoglobin drop exceeding 3 g/dl (or 10% of hematocrit), transfusion of 2 or more units of whole blood, packed red blood cells.²² The term low molecular weight heparins (LMWHs) used in the present study refers to both enoxaparin and dalteparin.

Route of Administration of LMWHs

All enoxaparin trials^{5,15–18,20} (Table 1) administered initial intravenous bolus of 30–40 mg. In the Assessment of the Safety and Efficacy of Thrombolytic Regimens (ASSENT) Plus trial, initial intravenous bolus of dalteparin was 30 IU/kg.¹⁹ After this, all subsequent injections of LMWHs were administered by subcutaneous route.

Statistical Analysis

The statistical analysis was performed by the Comprehensive Meta-Analysis software package (version CM 2.2, Biostat, Englewood, NJ). Heterogeneity of the studies was analyzed by the Cochran's Q statistics for each outcome. The studies were homogeneous ($p < 0.05$) for each outcome (including death, reinfarction, and major bleeding) when analyzed during index hospitalization at 7 d and 30 d. Therefore, the combined relative risks (RR) across all the studies and the 95% confidence intervals (CI) of death, myocardial infarction, and major bleeding (LMWHs versus UFH) were computed with using the Mantel-Haenszel fixed-effect model.^{23–24}

The purpose of the second meta-analysis was to analyze if any bias was introduced by the EXTRACT-TIMI 25 study. After excluding this study, the heterogeneity test for each outcome was repeated. The studies were homogeneous for each outcome, including major bleeding. Hence, the Mantel-Haenszel fixed-effect model was used. A two-sided alpha error < 0.05 was considered significant.

Results

Study Selection and Design

The 7 studies (Table 1) in this meta-analysis included randomized trials. The trials consisted of 27,577 patients

Table 1. Summary of Clinical Trials Used in the Meta-Analysis

Trial	N	LMWHs [†]	UFH [*]	Fibrinolysis	Aspirin	Primary outcome
ASSENT 3	4,078	Enoxaparin 30 mg IV then 1 mg/kg BID ≤ 7 d	60 u/kg bolus then 12 IU/kg per h for 48 h	TNK 30–50 mg (weight adjusted)	150–325 mg/d	In-hospital MI or RI or 30 d mortality
HART II	400	Enoxaparin 30 mg IV then 1 mg/kg Q 12 hrs for ≥ 72 hrs	4,000–5,000 IU bolus, then 15 IU/kg per h for ≥ 3 d	tPA weight adjusted over 90 min	NS	Angiographic 90 min TIMI flow
Baird et al. ¹⁷	300	Enoxaparin 40 mg IV then 40 mg TID for 4 d	5,000 IU bolus, then 30,000 IU over 24 h for 4 d	SK 1.5 MU or ASPAC 30 IU or tPA 100 mg	75–300 mg/d after day 4 [*]	MI, death, readmit for UA
ENTIRE-TIMI 23	242	Enoxaparin 30 mg IV then 1 mg/kg BID ≤ 8 d	60 u/kg bolus then 12 IU/kg per h for ≥ 3 d	TNK 0.53 mg/kg	100–325 mg/d [†]	Angiographic 60 min TIMI flow
ASSENT Plus	439	Dalteparin first dose 90 IU/kg then 120 IU/kg BID 4–7 d	4,000–5,000 IU bolus, then 800–1,000 IU/h for 48 h	tPA ≤ 100 mg over 90 min	150–325 mg/d	Angiographic TIMI flow
ASSENT 3 Plus	1,639	Enoxaparin 30 mg IV then 1 mg/kg BID ≤ 7 d	60 u/kg bolus then 12 IU/kg per h for ≥ 3 d	TNK 30–50 mg (weight adjusted)	100–325 mg/d [§]	In-hospital MI or RI or 30 d mortality
EXTRACT TIMI 25	20,506	Enoxaparin 30 mg IV then 1 mg/kg BID ≤ 8 d	60 u/kg bolus then 12 IU/kg per h for at least 48 h	STK/TNK/Tpa Alteplase or Reteplase	75–325 mg/d ^{**}	MI or RI at 30 d

^{*}No aspirin was given during the first 4 days.

[†]Initial dose of 160 mg PO or 250–500 mg IV was administered.

[§]Initial dose 150–325 mg/d.

^{**}Initially, 150 to 325 mg of aspirin orally or 500 mg intravenously unless had received at least 325 mg of aspirin within the prior 24 h.

Abbreviations: APSAC, anisoylated plasminogen-streptokinase activator complex (anistreplase); ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; HART, Heparin and Aspirin Reperfusion Therapy; LV, left ventricular; MI, myocardial infarction; MU, mega units; NS, not specified; RI, refractory ischemia; TIMI, thrombolysis in myocardial infarction; SK, streptokinase; TNK, tenecteplase; tPA, tissue plasminogen activator (alteplase); UA, unstable angina.

(LMWHs, $n = 13,846$; UFH, $n = 13,731$). Demographics and baseline characteristics were comparable between the 2 treatment groups, with no significant difference observed (Table 2).

Quality Assessment

All the trials reported adequate concealment of the randomized treatment sequence. In 6 studies, follow-up was at least 99% complete,^{6,15–18,20} in the remaining study completeness of follow-up was not reported.¹⁹

Clinical Outcome

Reinfarction and Death

Compared with to UFH, LMWH significantly reduced reinfarction (RR: 0.55; 95% CI: 0.47–0.63; $p < 0.001$) during hospitalization at 7 days (Figure 1) and the effect remained consistent at 30 days (RR: 0.67; 95% CI:

0.60–0.760; $p < 0.001$; Figure 2). When analyzed for mortality at 7 days (RR: 0.92; 95% CI: 0.84–1.02; $p = \text{NS}$ [not significant]; Figure 3) and 30 days (RR: 0.92; 95% CI: 0.85–1.0; $p = \text{NS}$; Figure 4) period, there were no statistically significant differences observed between the 2 groups.

Bleeding

The overall incidence of major bleeding events was significantly lower with UFH compared to LMWHs (RR: 1.40; 95% CI: 1.18–1.67, $p < 0.001$; Figure 5). Similarly the risk of minor bleeding was significantly lower among the UFH group as compared with the LMWH group (RR: 1.230; 95% CI: 1.132–1.337, $p < 0.0001$).

When analysis was done excluding TIMI-EXTRACT 25⁶ there was a trend favoring lower incidence of major bleeding

Table 2. Demographics and Baseline Characteristics of the Clinical Trials

Study	Design	Patients (N)	Eligibility	Follow-up
ASSENT 3	Open label	4,078	Age > 18 y; STEMI or LBBB, ≤6 h	30 d
HART II	Open label	400	Age > 18 y; STEMI or new LBBB, ≤12 h	5–7 d
Baird et al. ¹⁷	Open label	300	STEMI	90 d
ENTIRE TIMI 23	Open label	242	Age 21–75 y; STEMI, ≤6 h	30 d
ASSENT Plus	Open label	439	Age > 18 y; STEMI or new LBBB, ≤6 h	30 d
ASSENT 3 Plus	Open label	1,639	Age > 18 y; STEMI or LBBB, ≤6 h	30 d
EXTRACT TIMI 25	Double dummy	20,506	Age > 18 y; STEMI or LBBB, ≤6 h	30 d

Abbreviations: ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; HART, Heparin and Aspirin Reperfusion Therapy; LBBB, left bundle branch block; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

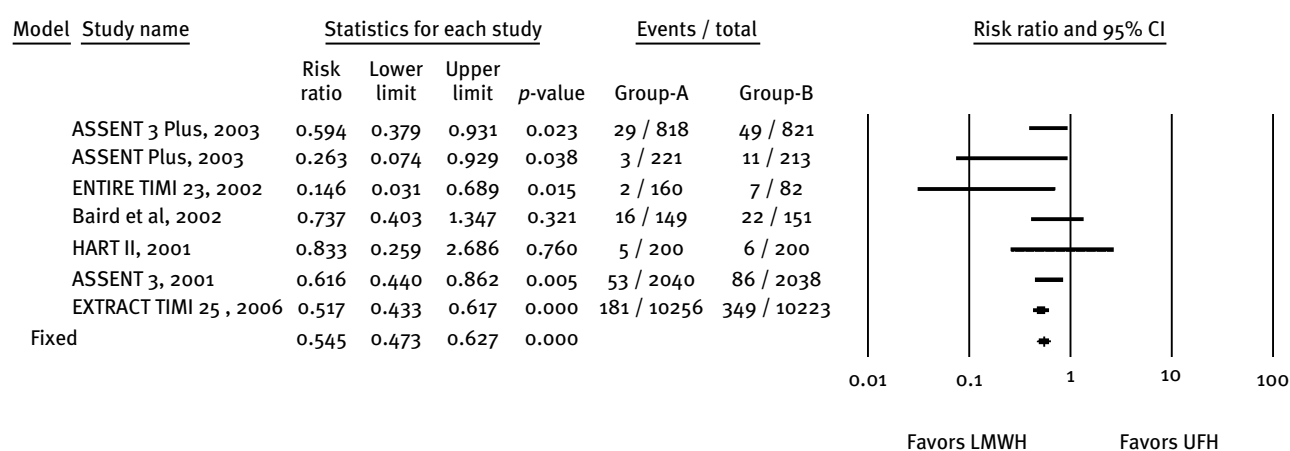


Figure 1. Relative risk of 7-day reinfarction: LMW heparin vs UF heparin. Abbreviations: ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; HART, Heparin and Aspirin Reperfusion Therapy; TIMI, thrombolysis in myocardial infarction.

with the use of UFH, but no significant difference between the 2 groups was observed (Figure 6).

Discussion

The results of our study suggest a benefit in using LMWH as opposed to UFH in the initial 7 days during hospitalization since the incidence of reinfarction is significantly lower in the LMWH group. There were 289 cases of reinfarction in the LMWH group as compared to 530 cases of reinfarction in the UFH group. The difference in the incidence of death was not significant at 7 days and at 30 days. But reinfarction was significantly lower in the LMWH group at 7 days and at 30 days follow-up. The overall incidence of a major bleeding event was significantly lower in the UFH group compared to LMWH (RR: 1.40; 95% CI: 1.18–1.67,

$p < 0.001$). Although there were more stroke events in the LMWH group as opposed to UFH, the difference was nonsignificant.

Antithrombin agents have shown to enhance the clot lysis after initial fibrinolytic therapy causing lower rate of recurrent myocardial infarction. The coronary artery patency rate is higher in patients given heparin therapy.²⁵ LMWH has a better antithrombotic effect and has a longer duration of action as compared to UFH. It is convenient to use due to its superior antithrombotic activities (more antifactor Xa activity than antifactor IIa activity).²⁶ This could probably explain the beneficial effects of LMWH when used along with fibrinolytic therapy as it prevents a rebound increase in thrombotic events which generally are observed after discontinuation of UFH. Also our analysis showed increased risk of bleeding with use of LMWH.

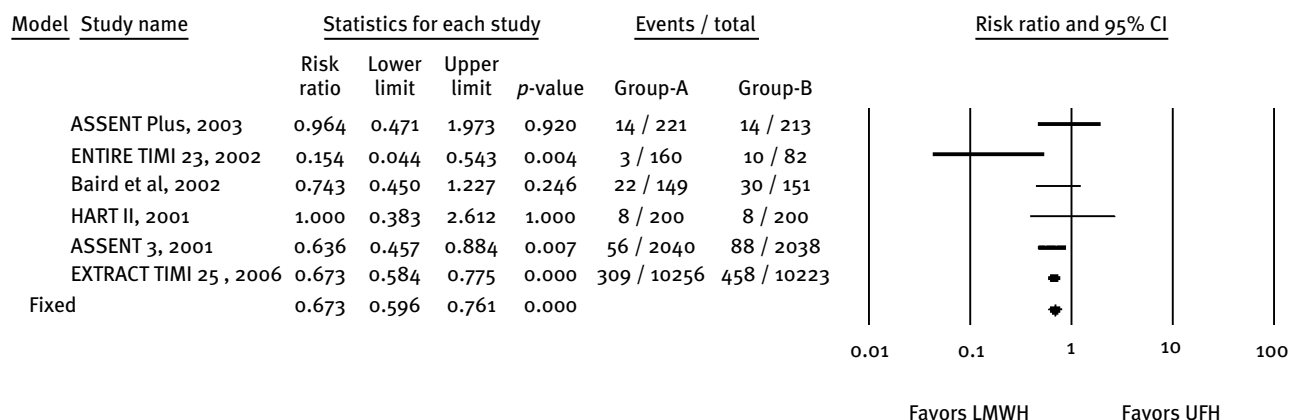


Figure 2. Relative risk of 30-days reinfarction: LMW heparin vs UF heparin. Abbreviations: ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; HART, Heparin and Aspirin Reperfusion Therapy; TIMI, thrombolysis in myocardial infarction.

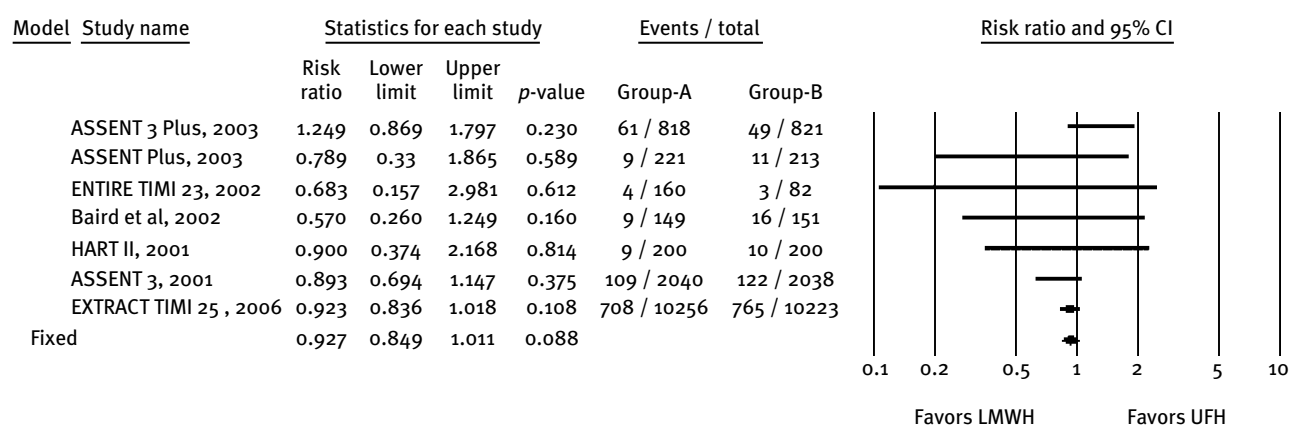


Figure 3. Relative risk of 30-days mortality: LMW heparin vs UF heparin. Abbreviations: ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; HART, Heparin and Aspirin Reperfusion Therapy; TIMI, thrombolysis in myocardial infarction.

On the contrary, Eikelboom et al., did not find the risk of bleeding was significantly higher in the LMWH group.⁵ This could be because of the fact that EXTRACT-TIMI 25 trial had a large number of patients ($n = 2532$) that were more than 75 years of age. The risk of bleeding is higher in patients of this age group as compared to the general population.

Unfortunately, conclusions regarding the optimum duration of the treatment of heparin cannot be drawn from this data. The different trials included in this study were heterogeneous in terms of duration of treatment with heparin. Some of the trials have treatment durations of 3 days while other trials have duration of up to 8 days. None of these studies have compared different duration of therapies. Studies comparing different durations of heparin therapy in treatment of STEMI are required

in the future to provide the appropriate duration of therapy.

In the ASSENT Plus trial,¹⁹ it is mentioned that clopidogrel/ticlopidine was given in 30% of patients receiving enoxaparin compared to 32% in the UFH group. In the ASSENT 3 Plus trial,²⁰ 55% of patients in the enoxaparin group received clopidogrel/ticlopidine therapy compared to 56% of patients in the UFH group. While in the Extract TIMI-25 trial,⁶ 27.2% of patients in the enoxaparin group compared to 28.7% of patients in the UFH group received clopidogrel therapy. In these 3 trials, the dosage, duration, and combination therapy of aspirin and clopidogrel therapy have not been clearly stated. Other than these three LMWH trials, none of the other trials have mentioned the administration of clopidogrel therapy in either group. In the presence of insufficient

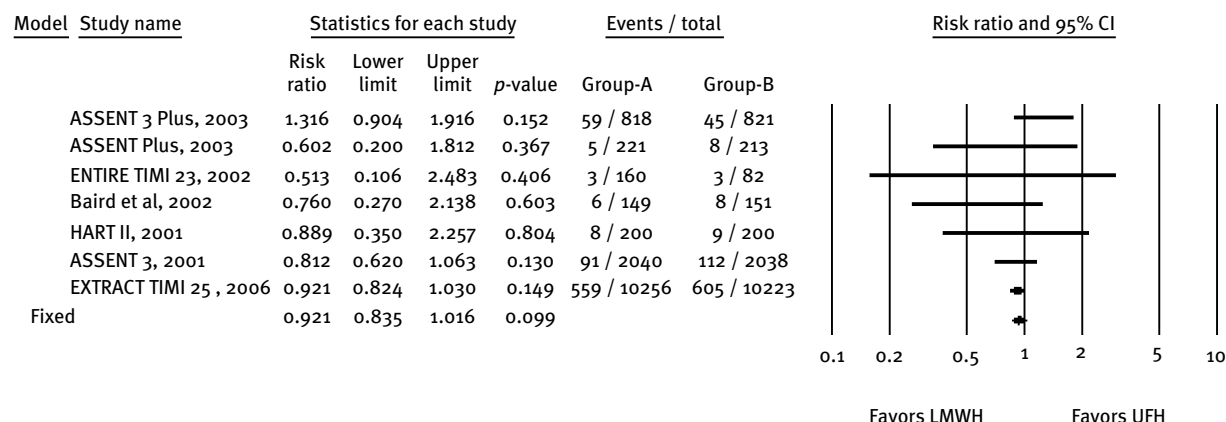


Figure 4. Relative risk of 7-day mortality: LMW heparin vs UF heparin. Abbreviations: ASSENT, Assessment of the Safety and Efficacy of Thrombolytic Regimens; ENTIRE, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy; EXTRACT, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment; HART, Heparin and Aspirin Reperfusion Therapy; TIMI, thrombolysis in myocardial infarction.

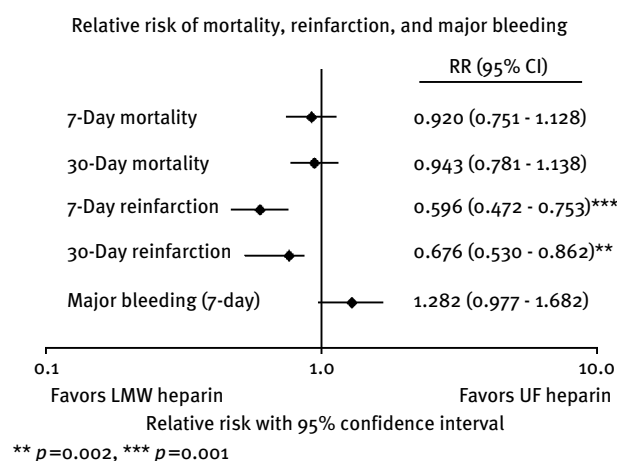


Figure 5. The overall incidence of major bleeding events was significantly lower with UFH compared with LMWHs (RR: 1.40; 95% CI: 1.18-1.67, $p<0.001$).

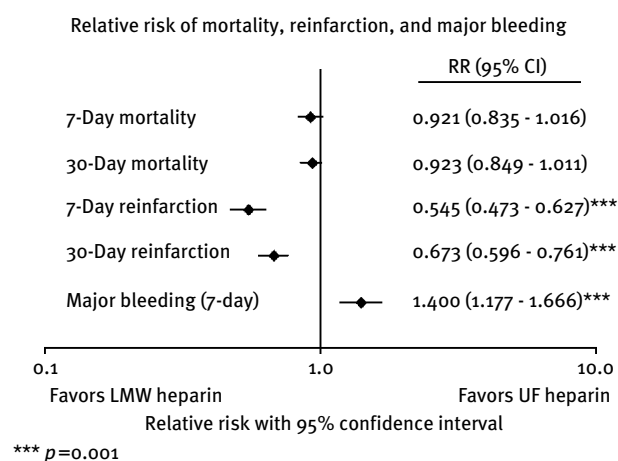


Figure 6. When analysis was done excluding TIMI-EXTRACT 25 6 there was a trend favoring lower incidence of major bleeding with the use of UFH but no significant difference between the 2 groups was observed.

evidence, no definitive conclusion regarding the use of clopidogrel therapy and increase in bleeding risk can be made.

Although our analysis has shown increased risk of bleeding with LMWH there was no significant increase in the rate of fatal intracranial hemorrhage. The significant decrease in the reinfarction rates at 7 days and 30 days may demonstrate an advantage of using LMWH as an adjunct to fibrinolytic therapy in treatment of STEMI.

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